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## Long-term Mortality in Patients with Thrombosis of the Inferior Vena Cava, Iliac and Femoral Veins

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**Objectives.** To assess the long-term mortality in patients with thrombosis of the vena cava, iliac and femoral veins.

**Design.** Registry study.

**Materials.** Between 1992 and 2000, 212 consecutive patients with acute pelvic vein thrombosis diagnosed by duplex sonography were examined by magnetic resonance imaging (MRI) to determine the most proximal extent of the thrombus. MRI revealed a thrombosis in the inferior vena cava in 46 patients (22%), in the iliac vein in 142 patients (67%), and in the femoral vein in 24 patients (11%).

**Methods.** The vital status of the patients was investigated in April 2004 using the Austrian National Registry and the Cause of Death Register.

**Results.** A total of 211 patients of the original 212 patients were monitored over a mean follow-up period of 91 months. Seventy-two of 211 patients (34%) had died. There was no significant difference in the long-term mortality, the survival period or the occurrence of fatal pulmonary embolism (PE) between previously diagnosed vena cava, iliac vein, or femoral vein thrombosis.

**Conclusions.** Extension of a thrombus into the inferior caval vein in patients considered to have a pelvic vein thrombosis has no impact on long-term mortality or the development of fatal PE compared to those patients with thrombus limited to more distal veins.

**Keywords:** Long-term mortality; Fatal pulmonary embolism; Survival; Inferior vena cava thrombosis; Follow-up.

### Introduction

Thrombotic involvement of the inferior vena cava is a common occurrence in patients with proximal deep vein thrombosis of the lower limb.<sup>1–4</sup>

In a previous study,<sup>4</sup> we showed by magnetic resonance imaging (MRI) that thrombus extends into the inferior vena cava in 22% of patients with a pelvic deep vein thrombosis diagnosed by duplex sonography. In our patients extension of thrombus into the inferior vena cava was not associated with a greater frequency of pulmonary embolism or higher mortality during hospitalisation or during an initial follow-up period of 4 weeks.

There was no difference in short-term mortality in our patients. However, long-term mortality in patients with inferior vena cava thrombosis is largely unknown.<sup>5,6</sup> The aim of the present follow-up study was to investigate the long-term mortality of this

condition in a consecutive series of patients who had been enrolled in our previous study.

### Material and Methods

#### Study background

Between 1992 and 2000, a consecutive series of 212 patients considered to have a deep vein thrombosis proximal to the inguinal ligament, diagnosed by duplex ultrasound, were investigated by magnetic resonance imaging (MRI) to assess the most proximal extent of the thrombus in the pelvic veins. The design, methods and results of this investigation were reported in a previous publication.<sup>4</sup> Using MRI to assess the most proximal extent of the thrombus in 212 patients, it was found that the deep vein thrombosis (DVT) extended into the inferior vena cava in 46 patients (22%), into iliac veins in 142 patients (67%), and was confined to the femoral veins in 24 patients (11%). The frequency of pulmonary embolism was

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unrelated to the proximal extent of the thrombus. All patients received subcutaneous low molecular weight heparin (Fragmin, Pharmacia, Stockholm, Sweden) at a dose of 100 IU/kg body weight twice daily followed by oral anticoagulation with coumarin (Marcoumar<sup>®</sup> from Roche, Basle, Switzerland). The treatment regime of oral anticoagulation was independent of the extent of the thrombus. Oral anticoagulation was continued for 6 months in patients with the first thrombotic event and without any risk factors such as a thrombophilia. Patients with recurrent thrombosis received oral anticoagulation for at least 1 year.

All patients were followed up for at least 4 weeks. During this period no patient died due to fatal pulmonary embolism.

#### *Follow-up investigation*

Follow-up studies were performed in April 2004 to investigate the vital status of all patients. For this purpose we used the personal identification number of every patient, which in Austria is a 10-digit code. We linked the patient's identification number with the nationwide Austrian Health Care Register and the Cause of Death Register to assess the vital status of the patients as well as the causes of death. The Austrian Cause of Death Register documents the dates and causes of all deaths in Austria. The causes of death until April 2004 were encoded according to the International Classification of Diseases (ICD-9 until the end of 2000, thereafter ICD-10), based on the data noted in the death certificates, which had been filled out by physicians, in hospitals, by general practitioners, or in forensic medicine. The follow-up period ended on April 1, 2004.

#### *Study population*

Of 212 patients included in the previous study, one was lost to follow-up because of emigration. The remaining 211 patients (100 men and 111 women) were followed up and included in the present study.

#### *Statistics*

All variables were summarised using frequency distributions for categorical variables and mean and standard deviation for continuous variables. Comparisons between groups were performed using Kruskal-Wallis-test or Mann-Whitney *U*-test for continuous variables and Chi-square-test for categorical variables. *p* values of  $\leq 0.05$  were considered statistically significant.

## **Results**

### *Patient characteristics*

In all, 211 of 212 patients (99.5%) (100 men and 111 women) were followed up. One patient with iliac vein thrombosis was lost to follow-up. The mean duration of follow-up was 91 months (range, 41–141 months). Patient characteristics are summarised in Table 1.

### *Long-term mortality*

Seventy-two (34%; 34 men, 38 women) of 211 patients died during the follow-up period. Fifteen of 46 patients (33%) with previously diagnosed inferior vena cava thrombosis died. Among 141 patients in whom iliac vein thrombosis was established by MRI, 48 (34%) died. Of 24 patients in whom the thrombus was confined to the femoral veins, nine (38%) died. There was no significant difference in long-term mortality between patients with previously diagnosed inferior vena cava thrombosis, iliac vein thrombosis or femoral vein thrombosis ( $p=0.88$ ).

The deaths occurred within 38 months of the previously diagnosed thrombo-embolic event; there was no significant difference between patients with previously diagnosed inferior vena cava, iliac vein, or femoral vein thrombosis ( $p=0.36$ ) (Table 1). The mean age of the deceased patients was 76 years (range, 30–96 years).

The causes of death were known in all cases. These included cardiac disease ( $n=19$ ), malignant disease ( $n=20$ ), myocardial infarction ( $n=10$ ), pneumonia ( $n=6$ ), ischaemic stroke ( $n=4$ ), multiple trauma ( $n=2$ ), fatal pulmonary embolism ( $n=9$ ) and fatal major bleeding ( $n=2$ ).

### *Fatal bleeding*

Fatal major bleeding occurred in two patients. One patient died because of rupture of an abdominal aneurysm 104 months following a femoral vein thrombosis. The other had fatal cerebral bleeding 9 months following iliac vein thrombosis. The latter patient was still receiving oral anticoagulant therapy at the time of death.

### *Fatal pulmonary embolism*

Only nine of 211 patients (4.3%) died because of fatal pulmonary embolism during the follow-up period. In

Table 1. Patient characteristics and long-term mortality

	Caval vein thrombosis	Iliac vein thrombosis	Femoral vein thrombosis	
Number of patients $n=212$	46 (22%)	142* (67%)	24 (11%)	
Deceased patients	15/46 (33%)	48/142 (34%)	9/24 (38%)	$p=0.88$
Survival period of deceased patients [months]	29	42	33	$p=0.36$
Follow-up period for survivors [months]	86	87	100	$p=0.17$
Fatal pulmonary embolism	2/46 (4.3%)	6/142 (4.2%)	1/24 (4.2%)	$p=0.99$
Major bleeding	0/46	1/142 (0.7%)	1/24 (4.2%)	

\* One patient was lost to follow-up.

six of these patients the diagnosis was verified by autopsy. In one patient fatal pulmonary embolism was accompanied by malignant disease at the time of death. In terms of medical history the fatal pulmonary embolism was the second thrombo-embolic event in the lives of three patients, the third event in the lives of another three patients, and the fourth event in the life of one patient. At the time of death three patients with fatal pulmonary embolism were still receiving anticoagulant therapy.

There was no significant difference in fatal pulmonary embolism between patients with previously diagnosed inferior vena cava, iliac vein, or femoral vein thrombosis ( $p=0.99$ ). With regard to mean survival, fatal pulmonary embolism occurred within an average of 18 months after previous DVT. This was significantly shorter than the mean survival of the remaining deceased patients ( $p=0.01$ ). The ages of those patients who died due to fatal pulmonary embolism were comparable with those of the other deceased patients ( $p=0.59$ ).

## Discussion

Since, thrombotic involvement of the inferior vena cava is a common occurrence in patients with proximal deep vein thrombosis of the lower extremity,<sup>1-4,7</sup> the aim of the present study was to investigate long-term mortality in patients with inferior caval vein thrombosis. The three principal findings of the present study are detailed in the following.

Firstly, there was no significant difference in long-term mortality between the patients with a previous inferior vena cava, iliac, or femoral deep vein thrombosis. In concurrence with the published literature, death was most commonly due to cancer, cardiovascular disease or myocardial infarction.<sup>8,9</sup> The overall long-term mortality rate of 34% within a mean follow-up period of 91 months is comparable with the rates reported in previous studies.<sup>8,10,11</sup>

Secondly, fatal pulmonary embolism occurred in nine of 211 patients (4.3%). This was comparable with previously published data.<sup>8-10,12-14</sup> The lowest rate of fatal PE was 1.5% observed by Douketis *et al.*<sup>12</sup> The highest rate of fatal PE was 4.5% observed by Decousus *et al.*<sup>9</sup> The relatively high rate of fatal PE in the present study is probably due to the higher autopsy rate compared to other studies.<sup>10,15</sup>

The mean survival of patients with fatal pulmonary embolism was significantly shorter than the mean survival of the other deceased patients. It should be noted that in the present study the frequency of pulmonary embolism was not increased among patients with previously diagnosed inferior vena cava thrombosis, although none of the previously enrolled patients received an inferior vena cava filter (IVF).

Third, major bleeding was a rare event in our study. Only two of 211 patients (0.95%) died because of fatal major bleeding; this finding concurs with previously published data.<sup>8,10,16</sup> In no case was major bleeding associated with the extent of the previously diagnosed DVT.

The present study has a number of limitations. Firstly, since patients with clinically massive pulmonary embolism who need intensive care were not included, the present findings may not apply to these patients. Secondly, the study is based on data from a registry. Detailed patient data concerning the development of recurrent DVT or the occurrence of post-thrombotic syndrome were not available. Furthermore, since the patients were studied at a single centre, a hospital-specific selection bias cannot be excluded.

The strengths of the study are its long follow-up period and the large patient sample. Studies investigating long-term survival in patients with inferior vena cava thrombosis are scarce.<sup>17</sup> The follow-up period is usually limited to 1-3 years;<sup>15,18</sup> a few studies extend to 8 years.<sup>8,11,19</sup> A further strength of the present study is that the general autopsy rate (34.7%) was higher than the rates reported in previous studies.<sup>15</sup>

In conclusion, the present investigation showed that the extension of thrombi into the inferior vena cava in patients considered to have a pelvic vein thrombosis has no impact on long-term mortality or the development of fatal pulmonary embolism within a mean follow-up period of 91 months.

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